PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 28 February 2001 (28.02.01)	
International application No. PCT/EP00/05542	**Applicant's or agent's file reference** 2475/002628
International filing date (day/month/year) 16 June 2000 (16.06.00)	**Priority date** (day/month/year) 24 June 1999 (24.06.99)
Applicant HEAL, David, John	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 January 2001 (12.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
2475/002628		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 05542	16/06/2000	24/06/1999
Applicant		
KNOLL AKTIENGESELLSCHAFT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PHARMACEUTICAL COMPOSITION CONTAINING SIBUTRAMINE AND ORLISTAT

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05542

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/365 //(A61K31/365,31:135)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EMBASE, CHEM ABS Data, CANCERLIT, EPO-Internal, MEDLINE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BUTTLE L.A.: "Anti-obesity drugs: On target for huge market sales" EXPERT OPINION ON INVESTIGATIONAL DRUGS(EXPERT OPIN. INVEST. DRUGS), 5/12 (1583-1587), 1997, XP002105328 United Kingdom page 1584, column 2, paragraph 5 -page 1586, column 2, paragraph 1 page 1587, column 1, paragraph 3 ---	1,2,4-8
A	WILDING, J.: "OBESITY TREATMENT" BRITISH MEDICAL JOURNAL (ENGLAND), V315, (OCT 18), P997-1000, 1997, XP002105329 page 999, column 2, paragraph 4 -page 1000, column 1, paragraph 2 --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 November 2000	15/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Leherte, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/05542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FINER N.: "Present and future pharmacological approaches" BRITISH MEDICAL BULLETIN(BR. MED. BULL.), 53/2 (409-432), 1997, XP002105330 United Kingdom page 422, paragraph 2 -page 423, paragraph 1 ---	1-8
P,X	WO 99 33450 A (KNOLL AG ;JACKSON HELEN CHRISTINE (GB); HEAL DAVID JOHN (GB)) 8 July 1999 (1999-07-08) the whole document -----	1-8

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/05542

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9933450 A	08-07-1999	AU 2273899 A	19-07-1999
		BR 9814498 A	10-10-2000
		EP 1039900 A	04-10-2000
		NO 20003313 A	11-08-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2475/002628		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05542	16/06/2000	24/06/1999
International Patent Classification (IPC) or national classification and IPC A61K31/365		
Applicant KNOLL AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/01/2001	02.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Tardi, C Telephone No. +49 89 2399 8180

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05542

I. Basis f th r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-13 as originally filed

Claims, No.:

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-3.

because:

   ☒ the said international application, or the said claims Nos. 1-3 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	4-8

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

R It m III

1) Claims 1-3 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

1) Reference is made to the following documents:
D1: BUTTLE L.A.: 'Anti-obesity drugs: On target for huge market sales' EXPERT OPINION ON INVESTIGATIONAL DRUGS(EXPERT OPIN. INVEST. DRUGS), 5/12 (1583-1587), 1997, XP002105328 United Kingdom
D2: WILDING, J.: 'OBESITY TREATMENT' BRITISH MEDICAL JOURNAL (ENGLAND), V315, (OCT 18), P997-1000, 1997, XP002105329
D3: FINER N.: 'Present and future pharmacological approaches' BRITISH MEDICAL BULLETIN(BR. MED. BULL.), 53/2 (409-432), 1997, XP002105330 United Kingdom

2) Novelty (Art. 33(2) PCT)
Although the three documents cited disclose sibutramine and orlistat as promising drugs for the treatment of obesity, none of the documents disclose their use in combination for the treatment of co-morbid conditions associated with obesity. Therefore, the subject-matter of claims 1-8 is new.

3) Inventive step (Art. 33(3) PCT)
3.1 The document D2 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses two drugs for obesity treatment: sibutramine, a serotonin and noradrenaline reuptake inhibitor and orlistat, a pancreatic lipase inhibitor which inhibits triglyceride digestion and therefore decreases fat absorption in the small intestine (p.999, second column, last paragraph). The subject-matter of claim 1 therefore differs from this in that the method of treatment of co-morbid conditions associated with obesity comprises the administration of both sibutramine and orlistat. The problem to be solved may therefore be

regarded as improving the treatment of obesity.
Nb. It does not seem pertinent to draw a distinction between the treatment of obesity and the treatment of co-morbid conditions associated with obesity, as it emerges from the prior art documents, that a treatment of obesity is considered efficient when it leads, among other, to a significant improvement in co-morbid conditions (D2, p.997, second column, second paragraph ; D3, Table 1 p.411)

D2 suggests that combinations of drugs with different modes of action may be required, as is currently the case with hypertension (p.997, second column, "possible futures of obesity treatment" and p.1000, first column, l.8-11). According to D2, with the withdrawal of dexfenfluramine (p.998, first column, l.2-8), sibutramine and orlistat are the two drugs under review for the treatment of obesity (p.999, second column, last paragraph). As they have different modes of action, it would have been obvious for the skilled person taking into account the teaching of D2 to consider their use in combination for the treatment of obesity. Therefore, the subject-matter of claim 1 does not appear to involve an inventive step.

3.2 The appended claims 2 and 3 are new but it is not apparent to which technical problem the administration of the compound of formula I 30 minutes to 3 h prior to the administration of the compound of formula II would provide an inventive solution.

3.3 The claims 4-8 are "first-" and "second-medical use" claims related to the method of treatment of claim 1, as such, they do not appear to involve an inventive step either.

4) 4.1 For the assessment of the present claims 1-3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4.2 The subject-matter of the present claims 4-8 fulfills the requirements of Art. 33(4) PCT regarding industrial applicability.

Re Item VI

1) Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99 33450	8 July 1999	16 December 1998	

Although this document does not belong to the state of the art in the sense of Rule 64.1(b) PCT, it might disclose all the features of claims 1-8.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00205 A1

(51) International Patent Classification[7]: A61K 31/365
// (A61K 31/365, 31:135)

(21) International Application Number: PCT/EP00/05542

(22) International Filing Date: 16 June 2000 (16.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9914744.9 24 June 1999 (24.06.1999) GB

(71) Applicant *(for all designated States except US)*: **KNOLL AKTIENGESELLSCHAFT** [DE/DE]; D-67061 Ludwigshafen (DE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **HEAL, David, John** [GB/GB]; R3 Pennyfoot Street, Nottingham NG1 1GF (GB).

(74) Agent: **DOERPER, Thomas**; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).

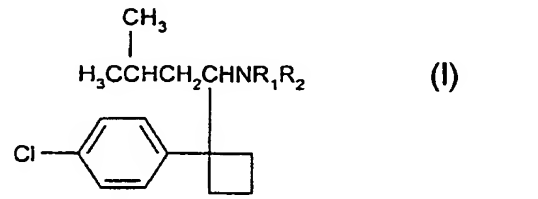
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

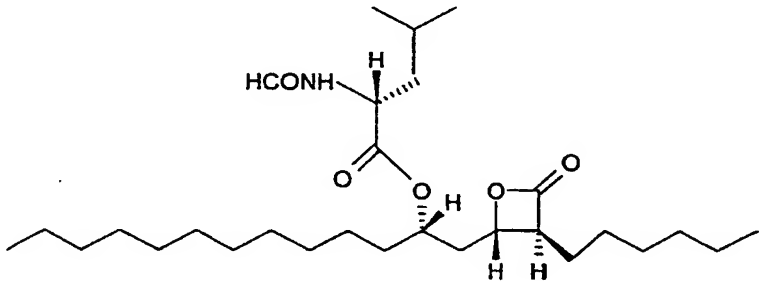
Published:
— *With international search report.*

[Continued on next page]

(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING SIBUTRAMINE AND ORLISTAT



(I)



(II)

(57) Abstract: A method for the treatment of co-morbid conditions associated with obesity in a human in need of such treatment which comprises administration to the human of a therapeutically effective amount of a compound of formula (I) including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and a therapeutically effective amount of a compound of formula (II) wherein the compound of formula (I) and the compound of formula (II) are administered simultaneously, separately or sequentially.

WO 01/00205 A1

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PHARMACEUTICAL COMPOSITION CONTAINING SIBUTRAMINE AND ORLISTAT

This invention relates to a method for treating and preventing co-morbid conditions associated with obesity and to products and pharmaceutical compositions suitable for use in such a method. More particularly, the invention relates to a method for the treatment of co-morbid conditions associated with obesity by the administration of sibutramine or a salt or a metabolite thereof and orlistat and to products and compositions containing such compounds.

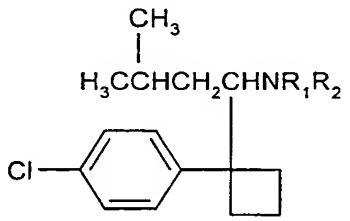
Sibutramine hydrochloride monohydrate and orlistat are both currently being developed for use in the treatment of obesity. The two compounds, however, achieve weight loss through entirely different mechanisms.

Sibutramine is a 5-hydroxytryptamine and noradrenaline reuptake inhibitor *in vivo* (Buckett, W.R., Thomas, P.C. & Luscombe, G.P. (1988). Prog. Neuro-Psychopharmacol. Biol. Psychiat. 12, 575-584 and Luscombe, G.P., Hopcroft, R.H., Thomas, P.C. & Buckett, W.R. (1989). Neuropharmacology, 28, 129-134.) Studies have shown that it reduces body weight by a dual mode of action; it decreases food intake by enhancing satiety (Fantino, M. & Souquet, A.-M. (1995). Int. J. Obesity, 19, 145; Halford, J.C.G., Heal, D.J. & Blundell, J.E. (1995). Brit. J. Pharmacol. 114, 387P; and Stricker-Krongrad, A., Souquet, A.-M. & Burlet, C. (1995). Int. J. Obesity, 19, 145.), and it increases energy expenditure by stimulating thermogenesis (Connoley, I.P., Heal, D.J. & Stock, M J. (1995). Brit. J. Pharmacol. 114, 388P; and Connoley, I P., Frost, I., Heal, D.J. & Stock, M.J. (1996). Brit. J. Pharmacol. 117, 170P).

Orlistat inhibits lipase enzymes which are responsible for breaking down ingested fat (Borgstrom, B. (1988). Biochem. Biophys. Acta. 962 (3), 308-316); as a consequence of this, unabsorbed fat is egested in the faeces.

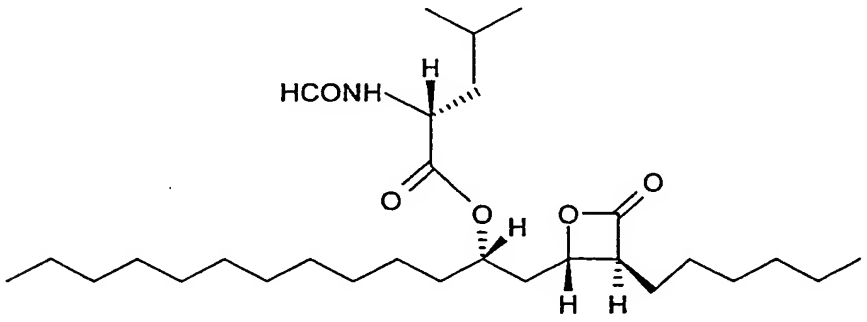
It has been reported that orlistat should not be combined with appetite suppressants (The New York Times May 15 1997) . Surprisingly, it has now been found that co-administration of sibutramine hydrochloride monohydrate and orlistat results in beneficial effects with respect to weight-loss.

Accordingly, the present invention provides a method for the treatment of co-morbid conditions associated with obesity in a human in need of such treatment which comprises administration to the human of a therapeutically effective amount of a compound of formula I



I

including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and a therapeutically effective amount of a compound of formula II



II

wherein the compound of formula I and the compound of formula II are administered simultaneously, separately or sequentially.

The present invention may provide the following advantages. Firstly, the beneficial effect achieved is greater than that achieved by the sole administration of either a compound of formula I or compound II. Secondly, a synergistic effect is achieved in which the benefit obtained by the administration of a compound of formula I and the compound of formula II to a first test group is greater than the total benefit achieved by administration of the compound of formula I to a second test group and the benefit achieved by administration of compound II to a third test group. Thirdly, when the benefit obtained after administration of either a compound of formula I or the compound II has reached a plateau, a further benefit is achieved by administering the other compound. Fourthly, lower doses of the compound of formula I and the compound of formula II may be used in the present invention thus

reducing the side-effects associated with administration of a higher dose of each compound.

The term "co-morbid conditions associated with obesity" as used in this document means medical conditions known to those skilled in the art to be associated with obesity. The term includes but is not limited to the following: diabetes including non-insulin dependent diabetes mellitus, impaired glucose tolerance, hypertension, coronary thrombosis, stroke, depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, lipid syndromes, hyperglycaemia, hyperlipidaemia, and stress in mammals particularly humans.

In addition the present invention may be useful in the treatment or prevention of metabolic diseases and conditions arising therefrom, for example non exercise activity thermogenesis and increased metabolic rate, sexual dysfunction, sleep apnoea, premenstrual syndrome, urinary incontinence including stress incontinence, hyperactivity disorders, hiatial hernia and reflux esophagitis, pain, especially neuropathic pain, weight gain associated with drug treatment, chronic fatigue syndrome, osteoarthritis and gout, cancers associated with weight gain, menstrual dysfunction, gallstones, orthostatic hypotension and pulmonary hypertension.

The present invention may be useful in preventing cardiovascular disease, and in reducing platelet adhesiveness, in aiding weight loss after pregnancy,reducing the craving to smoke and in aiding weight loss after smoking cessation. The present invention may also be useful in lowering uric acid levels and lipid levels in mammals particularly humans.

A preferred compound of formula I is N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine or a salt thereof, for example the hydrochloride salt, known as sibutramine hydrochloride. A preferred form of this hydrochloride is its monohydrate, known as sibutramine hydrochloride monohydrate.

The preparation and use of compounds of formula I, such as N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof, in the treatment of depression is described in British Patent Specification 2098602. The use of compounds of formula I such as N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof in the treatment of Parkinson's disease is described in published PCT application WO 88/06444. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof in the treatment of cerebral function disorders is described in US Patent 4939175. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine hydrochloride in the treatment of obesity is described in European Patent Number 397831. A particularly preferred form of this compound is N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine hydrochloride monohydrate (sibutramine hydrochloride monohydrate) which is described in European Patent Number 230742. The use of N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine and salts thereof for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus is described in published PCT application WO95/20949.

The compound of formula II has the chemical name (2*S*, 3*S*, 5*S*)-5-[(*S*)-2-formamido-4-methylvaleryloxy]-2-hexyl-3-hydroxyhexadecanoic acid lactone. It is also known as "N-formyl-L-leucine, ester with (3*S*, 4*S*)-3-hexyl-4-[(2*S*)-2-hydroxy-tridecyl]-2-oxetanone", (-)-tetrahydrolipstatin, tetrahydrolipistatin, and orlistat.

The extraction and use of orlistat in the control or prevention of obesity and hyperlipaemia is described in US Patent 4598089 (Hoffmann-La Roche Inc.). A process for the preparation of orlistat is described in US Patent 4983746 (Hoffmann-La Roche Inc.). A composition comprising orlistat and acarbose is described in EP638317 (Hoffmann-La Roche AGF).

It will be appreciated by those skilled in the art that compounds of formula I contain a chiral centre. When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms. The present invention includes the use of the individual enantiomers and mixtures of the enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of

diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. Enantiomers of secondary and tertiary amines of formula I can also be prepared by preparing the primary amine racemate, resolving this mixture into its individual enantiomers and then converting the relevant optically pure primary amine enantiomer into the desired secondary or tertiary amine product.

Preferred compounds of formula I are N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N- methylamine, and N-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine including racemates, individual enantiomers and mixtures thereof, and pharmaceutically acceptable salts thereof. Specific enantiomers offormula I are (+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, (-)-N-{1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl}-N,N-dimethylamine, (R)-(+)-N-{1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl}-N-methylamine, (S)-(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine, (R)-(+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and (S)-(-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine.

In the method of the present invention a compound of formula I and the compound of formula II may be administered concomitantly or concurrently, for example in the form of separate dosage units to be used simultaneously, separately or sequentially.

In another aspect the present invention provides a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

In yet another aspect the present invention provides a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II as a combined preparation for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

In a further aspect the present invention provides a product containing a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II as a combined preparation for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

In yet another aspect the present invention provides the use of a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl in the manufacture of a medicament for the treatment of co-morbid conditions associated with obesity in a patient who is also receiving treatment with orlistat.

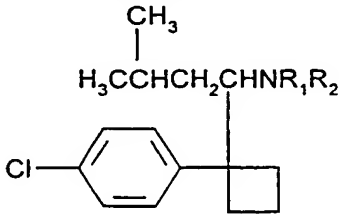
In a further aspect, the present invention provides a method of treating co-morbid conditions associated with obesity comprising the administration of an adjunctive therapy comprising a therapeutically effective amount of a compound of formula I and orlistat to a patient in need thereof.

The invention also provides the use of the above combination of drugs in the manufacture of a medicament for the treatment of co-morbid conditions associated with obesity. Additionally, it provides the combination for use in the treatment of co-morbid conditions associated with obesity.

The amount of each compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound of formula I to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses and more preferably 10 mg, 15 mg, 20 mg, 25 mg or 30 mg per day and most preferably 20 mg. The dosage of orlistat to be administered will be in the range of 50 to 1440 mg given in one or more doses, preferably three times daily, more preferably in the range of 120 to 720 mg and most preferably in the range of 120 to 360 mg . The compound of formula I, preferably sibutramine hydrochloride monohydrate, may be administered in any of the known pharmaceutical dosage forms. Orlistat is preferably administered orally.

In a preferred aspect of the present invention sibutramine hydrochloride monohydrate is administered once daily, preferably first thing in the morning, and orlistat is administered three times daily either with or before meals. Preferably the dose of sibutramine hydrochloride monohydrate is 20 mg or 30 mg administered once daily and the dose of orlistat is 120 mg administered three times daily either with or before meals. Most preferably the dose of sibutramine hydrochloride monohydrate is given prior to the first dose of orlistat, preferably in the range of30 minutes to 3 hours, for example 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours or 3 hours, before the first dose of orlistat.

In another aspect of to the present invention there is provided a pharmaceutical composition comprising a compound of formula I



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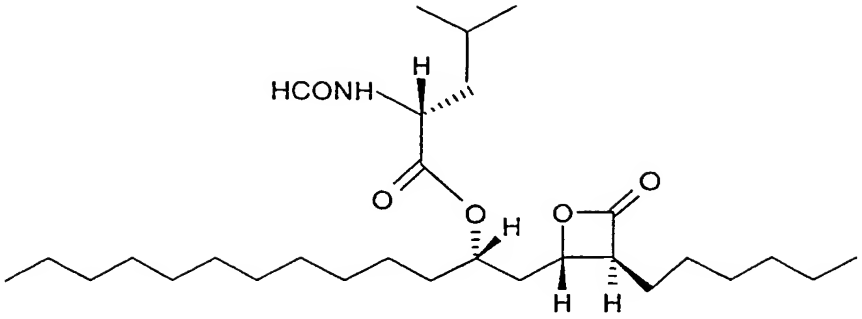
including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and the compound of formula II



II

in conjunction with a pharmaceutically acceptable diluent or carrier.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compounds with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 50 mg of the compound of formula I and 1 to 360 mg of orlistat.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compounds in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxy-methylcellulose,

and oily suspensions containing the active compounds in a suitable vegetable oil, for example arachis oil. The active compounds may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The compounds of formula I and orlistat may be formulated into a composition which the patient retains in his mouth so that the active compounds are administered through the mucosa of the mouth.

Dosage forms of the compounds of formula I suitable for rectaladministration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms of the compounds of formula I suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms of the compounds of formula I for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of each active compound contained in a topical formulation should be such that a therapeutically effective amount of each compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be

administered from a pump pack or from a pressurised pack containing a volatile propellant.

The compound of formula I may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compounds to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the compounds to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compounds to be infused. The support may be a single body containing all the compounds or a series of several bodies each containing part of the compounds to be delivered. The amount of active compounds present in an internal source should be such that a therapeutically effective amount of each compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compounds may, if desired, be associated with other compatible pharmacologically active ingredients. Optionally vitamin supplements may be administered with the compounds of the present invention.

Pharmaceutical compositions incorporating both a compound of formula I and orlistat are important embodiments of the present invention. Such pharmaceutical compositions contain a therapeutically effective amount of each of the compounds. Each dosage unit may contain the daily doses of both compounds, or may contain a fraction of the daily dose, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compound. In such case, the patient would daily take one of the

combination dosage units, and one or more units containing only the other compound.

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes either or both compounds of the invention unless otherwise stated.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinyl-pyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

Enteric coated tablets

Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories (Compound of formula I only)

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Sibutramine hydrochloride monohydrate	20
Orlistat	120
Starch	200
Magnesium stearate	10
Total	350

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Sibutramine hydrochloride monohydrate	10
Orlistat	120
Microcrystalline Cellulose	400
Silica	10

	Quantity (mg/tablet)
Stearic acid	5
Total	545

The components are blended and compressed to form tablets each weighing 545 mg.

The advantages of the present invention may be demonstrated by animal models or clinical trials as known to those skilled in the art. Suitable animal models and methods for clinical trials may be found in :

(1). "New Antidiabetic drugs" Eds CJ Bailey & PR Flatt 1990 Smith-Gordan and company Ltd, UK

(2). "Obesity" Eds P Bjorntorp & BN Brodoff, 1992, JB Lippincott Company, Philadelphia, USA and

(3). "Obesity: Trends and Treatments" S Parker 1996 Scrip Report, PJB Publications Ltd

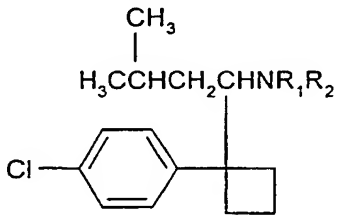
and references therein.

Studies are performed in which a compound of formula I is administered to a first test group, a compound of formula II is administered to a second test group, a combination of a compound of formula I and a compound of formula II is administered to a third test group with appropriate controls to eliminate the effects of the dosing vehicles used.

A statistical analysis of the effects achieved in each group provides results demonstrating the advantage of the present invention.

Claims

1) A method for the treatment of co-morbid conditions associated with obesity in a human in need of such treatment which comprises administration to the human of a therapeutically effective amount of a compound of formula I



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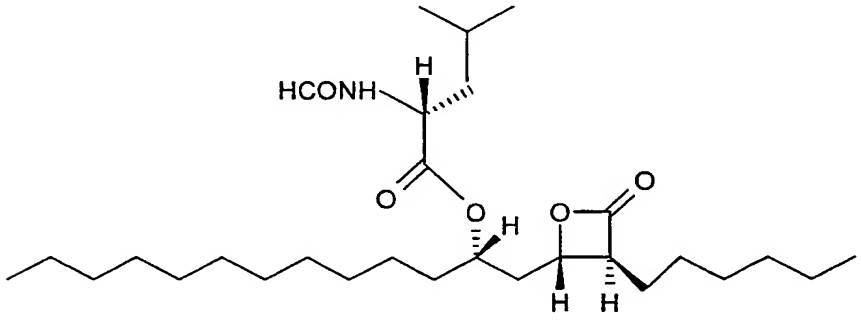
including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and a therapeutically effective amount of a compound of formula II



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wherein the compound of formula I and the compound of formula II are administered simultaneously, separately or sequentially.

2) A method according to claim 1 in which the compound of formula I is N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine or a salt thereof.

3) A method according to claim 2 wherein the compound of formula I is administered 30 minutes to 3 hours prior to the administration of the compound of formula II.

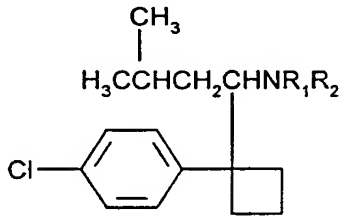
4) A compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

5) A compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II as a combined preparation for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

6) A product containing a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl and the compound of formula II as a combined preparation for simultaneous, separate or sequential use for the treatment of co-morbid conditions associated with obesity.

7) The use of a compound of formula I including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl in the manufacture of a medicament for the treatment of co-morbid conditions associated with obesity in a patient who is also receiving treatment with orlistat.

8) A pharmaceutical composition comprising a compound of formula I



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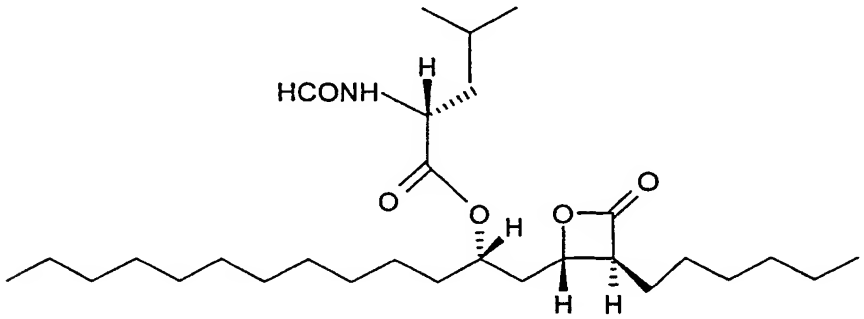
including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, and the compound of formula II



II

in conjunction with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

Internat[illegible]lication No
PCT/EP 00/05542

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/365 //(A61K31/365,31:135)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EMBASE, CHEM ABS Data, CANCERLIT, EPO-Internal, MEDLINE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BUTTLE L.A.: "Anti-obesity drugs: On target for huge market sales" EXPERT OPINION ON INVESTIGATIONAL DRUGS(EXPERT OPIN. INVEST. DRUGS), 5/12 (1583-1587), 1997, XP002105328 United Kingdom page 1584, column 2, paragraph 5 -page 1586, column 2, paragraph 1 page 1587, column 1, paragraph 3 ---	1,2,4-8
A	WILDING, J.: "OBESITY TREATMENT" BRITISH MEDICAL JOURNAL (ENGLAND), V315, (OCT 18), P997-1000, 1997, XP002105329 page 999, column 2, paragraph 4 -page 1000, column 1, paragraph 2 ---	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 November 2000	15/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FINER N.: "Present and future pharmacological approaches" BRITISH MEDICAL BULLETIN(BR. MED. BULL.), 53/2 (409-432), 1997, XP002105330 United Kingdom page 422, paragraph 2 -page 423, paragraph 1 ---	1-8
P,X	WO 99 33450 A (KNOLL AG ;JACKSON HELEN CHRISTINE (GB); HEAL DAVID JOHN (GB)) 8 July 1999 (1999-07-08) the whole document -----	1-8

INTERNATIONAL SEARCH REPORT

Internat[illegible]lication No
PCT/EP 00/05542

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9933450 A	08-07-1999	AU 2273899 A	19-07-1999
		BR 9814498 A	10-10-2000
		EP 1039900 A	04-10-2000
		NO 20003313 A	11-08-2000